

## Distributed Mathematical Model of Vasopressin in Patients with Severe Brain Injury

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### ABSTRACT

Disorders of water and sodium balance are frequently seen in patients with severe brain injury (SBI), and may worsen their prognosis. AVP serum levels remained within the normal range in SBI patients (either traumatic or non-traumatic), although tended to be greater in non-survivor than in survivor patients. AVP serum levels remained within the normal range values in these SBI patients, but those who died have shown higher incidence of abnormal sodium and water balance during the first week post-injury. We applied this to the steady-state availability of systems with times to outages and recoveries that are generally distributed. Also we provide the steady-state availability for a system subject to unplanned outages, for which times-to-outages are exponentially distributed and planned outages for which times-to outages have bounded distributions to check the damage of the hormonal levels.

**Keywords:** Vasopressin, SBI, TTP, Availability

### I. NOTATIONS

A-Steady-state system availability

$\lambda$ - Rate of failures (unplanned outages)

$\mu$ - Repair rate for unplanned outage

$\mu_2$ -Upgrade rate for planned outage

TTP-Time to planned outage.

TTU-Time to planned upgrade.

### II. MATHEMATICAL MODEL

For some electronic components, the hazard function of TTF has a bathtub curve is a monotonically decreasing function initially, eventually becoming a constant, and finally changing to a monotonically increasing function after sufficient time elapses. In other words, an exponential distribution (constant hazard function) holds only during one particular phase of the component life. For the planned outage, e.g., upgrading the hardware or software of the computer systems, the time between two consecutive upgrades is nearly deterministic, and even the time used to upgrade the system is nearly deterministic. Amenable to analytic treatment and numerical computation, the exponential assumption dominates academic research and industrial practices for evaluating system reliability and availability.

#### System with planned and unplanned outages

The system has 2 types of outages: planned and unplanned.

Unplanned outages could be caused by unanticipated system failures.

Planned outages can be system upgrades, maintenance, configuration change, etc., that are

scheduled to enhance system functionalities. TTP and TTU can follow general distributions. The objective is to derive a general formula of A, and to obtain availability bounds when TTP

Distributions are given with insufficient information.

The state of the system which is in 1 of the 3 states:

- State 0: the system is working perfectly;
- State 1: the system is under repair following an unplanned failure;
- State 2: the system is undergoing a scheduled upgrade.

Theorem 1: The steady-state availability of a system with unplanned and planned outages is:

$$A = \left[ 1 + \frac{\lambda}{\mu} + \frac{\lambda}{\mu_2} \cdot \frac{\alpha(\lambda)}{1-\alpha(\lambda)} \right]^{-1}$$
$$= \left[ 1 + \frac{\lambda}{\mu} + \theta(\lambda) \cdot \frac{\lambda}{\mu_2} \right]^{-1}$$

$$\alpha(\lambda) \equiv \int_0^{\infty} \exp(-\lambda \cdot x) dF(x)$$

$$\theta(\lambda) \equiv \frac{\alpha(\lambda)}{1-\alpha(\lambda)}$$

$$\mu^{-1} \equiv \text{MTTU} = \int_0^{\infty} x dG(x).$$

Because  $\lambda$  is a positive real number, then  $\alpha(\lambda)$  can be interpreted as  $P_r$ ( a planned outage occurs when the system is in the working state) .The complementary probability,  $1- \alpha(\lambda)$  , is  $P_r$ ( working system has an unplanned outage ) [3, 5 ].

Then  $\alpha(\lambda)$  has the properties:

- 1) If  $\lambda_1 > \lambda_2 > 0$ , then  $\alpha(\lambda_1) < \alpha(\lambda_2)$ :  $\alpha(\lambda)$  is a monotonically Decreasing function;
- 2)  $\alpha(0) = 1, \alpha(\infty) = 0, 0 \leq \alpha(\lambda) \leq 1$ .

It follows that  $\theta(\lambda)$  is also a monotonically decreasing function of  $\lambda$ .

Now, the Availability formula for the distribution of TTP is deterministic

Let TTP = T,

$$A_D(T) = \left[ 1 + \frac{\lambda}{\mu} + \frac{\lambda}{\mu_2} \cdot \frac{\exp(-\lambda T)}{1 - \exp(-\lambda T)} \right]^{-1}$$

$$= \left[ 1 + \frac{\lambda}{\mu} + \frac{\lambda}{\mu_2} \cdot \frac{1}{\exp(-\lambda T) - 1} \right]^{-1}$$

also, let TTP  $\in [T_1, T_2]$  ( $0 < T_1 < T_2$ ); the pdf of TTP is defined in such a way that  $f(x) = 0$ , for  $x$  not in  $[T_1, T_2]$  and  $\int_{T_1}^{T_2} f(x) dx = 1$ .

Let  $A_B(T_1, T_2)$  be the system availability, with a distribution of TTP bounded [6] in  $[T_1, T_2]$ . Hence, the availability bound for the deterministically distributed outages is,  
 $A_D(T_1) \leq A_B(T_1, T_2) \leq A_D(T_2), \quad 0 \leq T_1 \leq T_2$ .

### III. APPLICATION

Patients with severe brain injury (SBI), such as traumatic brain injury (TBI), hemorrhagic stroke (HS), ischemic stroke (IS) and subarachnoid hemorrhage (SAH) frequently have abnormal arginine-vasopressin (AVP) secretion. Various investigations has measured AVP in plasma and in cerebrospinal fluid (CSF) in patients with SBI and reported high levels, suggesting that increased AVP secretion may contribute to increase the primary lesion severity. Other investigations have suggested that AVP serum levels may affect the mechanisms of cardiovascular regulation of cerebral edema. In a previous study<sup>5</sup>, we compared AVP serum levels of healthy individuals with those of patients with SBI or brain death, and found a great variation in AVP values in the group with SBI, but no significant differences in mean plasma AVP levels between the three groups. A negative correlation between plasma osmolality and sodium was also found, suggesting the presence of syndrome of inappropriate antidiuretic hormone secretion (SIADH) in SBI group. Disorders of the sodium/water balance, particularly *diabetes insipidus* (DI) and SIADH, are common complications reported in the acute phase of SBI<sup>[1, 2, 7]</sup>, either traumatic brain injury or stroke, and contribute to the high morbidity and mortality observed in these patients<sup>6,7</sup>. Moderate and occasionally severe hyponatremia has been reported in around 30% of neurosurgical patients with SAH. The decrease in serum sodium was progressive, leading to neurological problems, such as confusion, lethargy, convulsions and, finally, coma.

Hyponatremia was first reported in 1950 in patients with SBI. Excessive natriuresis was observed and the term "cerebral salt-wasting syndrome" was coined<sup>9</sup>. The hypothesis of the natriuretic factor was not raised and, following the discovery of the antidiuretic hormone, SIADH was mentioned as the causal mechanism of hyponatremia in patients with SBI. The pathophysiology of the secretion and liberation of AVP and the mechanisms involved in sodium and water disorders in patients with acute severe brain lesion have not been adequately clarified. In many studies increased levels of AVP have been found and it has been suggested that this increase, in the early stages of the injury, may be of significant importance in the pathogenesis of cerebral edema.

### IV. METHODS

Severe brain injured group was composed of 36 patients, both sexes, aging  $\geq 18$  years, with initial Glasgow Coma Scale (GCS) score  $\leq 8$ , and an estimated time of injury  $\leq 72$  hours, enrolled non-consecutively. Exclusion criteria were: aging  $< 18$  years; associated major thoracic or abdominal trauma; sepsis; irresponsive circulatory shock; patients pregnant or lactating; previous history of chronic corticosteroids, thyroid hormone or desmopressin use, physical signs suggestive of brain death or clinical death during the observation period. Laboratory data of 29 healthy volunteers, previously reported served as control.

In the SBI patients, 10 mL blood samples were drawn on the 1st (D1), 2nd (D2), 3rd (D3) and 5th day (D5) post-inclusion for measuring AVP and serum osmolality, using a previously placed venous catheter. A 3 ml arterial blood sample was also collected for gas analysis, electrolytes, hemoglobin, hematocrit, lactate and glucose, using a previously placed arterial catheter. An isolated urinary sample at D1 and 24 hour urinary samples at D2, D3 and D5 were used for sodium and osmolality measurements. Blood samples (10 ml) for measurement of urea, creatinine and for carrying out a leukocyte count were collected only once (at D1). All samples were sent to specific laboratories for immediate evaluation, except the AVP sample. At the time of blood sampling for AVP measurement, the following clinical parameters were recorded: systemic blood pressure (SBP), central venous pressure (CVP), heart rate, urinary output and body temperature. During data collection, the volumes and types of fluid infused into the patients in the preceding 24 hours were registered for calculating the quantity of sodium that has been administered. Simultaneously, twenty-four hour urine collection was carried out, stored at 4°C and sent for measurement of urinary sodium. Sodium balance was then calculated at D2, D3 and D5<sup>[4, 8]</sup>.

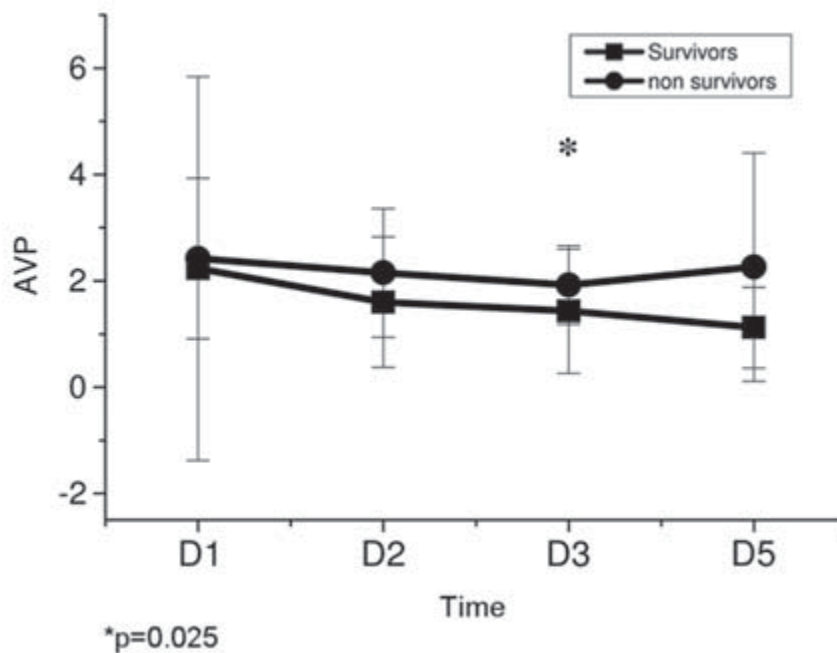
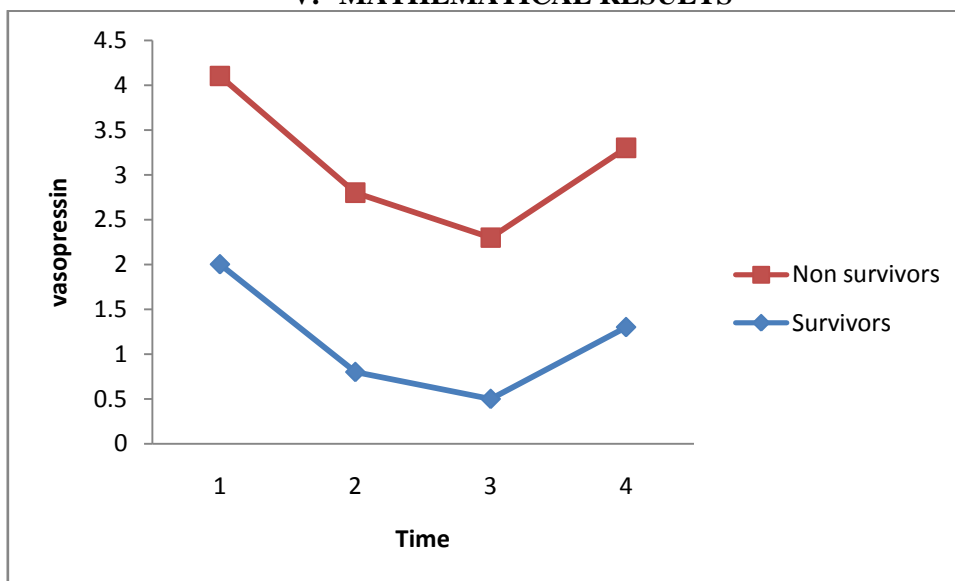


Fig 1. Vasopressin serum levels in survivors and non-survivors.

### V. MATHEMATICAL RESULTS



### VI. CONCLUSION

Plasma levels of AVP in healthy individuals at rest are usually very low. There was a slight variability of serum AVP levels in patients with SBI, seen as isolated plasmatic peaks, but their mean values always remained within the normal range, and these levels tended to decrease over time, both in survivors and non-survivors. Serum sodium and plasma osmolality have shown great variations in patients with SBI, and non-survivors have shown

greater and more significant deviations from normal values than those who survived. We found that the vasopressin levels of non survivors were increased.

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